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Long-term cognitive and academic outcomes among pediatric brain tumor survivors treated with proton versus photon radiotherapy

Amanda E. Child[1] | Emily A. Warren[2] | David R. Grosshans[3] | Arnold C. Paulino[3] | M. Fatih Okcu[4] | M. Douglas Ris[2] | Anita Mahajan[5] | Jessica Orobio[8] | Paul T. Cirino[6] | Charles G. Minard[7] | Andres G. Viana[6] | Johanna Bick[6] | Steven P. Woods[6] | Murali Chintagumpala[4] | Lisa S. Kahalley[2]

[1] Department of Neuropsychology, Kennedy Krieger Institute, Baltimore, Maryland, USA

[2] Department of Pediatrics, Section of Psychology, Baylor College of Medicine, Houston, Texas, USA

[3] Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[4] Department of Pediatrics, Section of Hematology Oncology, Baylor College of Medicine, Houston, Texas, USA

[5] Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, USA

[6] Department of Psychology, University of Houston, Houston, Texas, USA

[7] Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, Texas, USA

[8] Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence
Lisa S. Kahalley, Texas Children's Hospital, 1102 Bates Ave, Suite 940, Houston, TX 77030, USA.
Email: Kahalley@bcm.edu

Amanda E. Child and Emily A. Warren contributed equally to the present work.

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Abstract

Background: Proton radiotherapy (PRT) may be associated with less neurocognitive risk than photon RT (XRT) for pediatric brain tumor survivors. We compared neurocognitive and academic outcomes in long-term survivors treated with XRT versus PRT.

Methods: Survivors underwent neurocognitive evaluation >1 year after craniospinal (CSI) or focal PRT or XRT. Groups were compared using separate one-way analyses of covariance for the CSI and focal groups.

Results: PRT ($n = 58$) and XRT ($n = 30$) subgroups were similar on gender (66% male), age at RT (median = 6.5 years), age at follow-up (median = 14.6 years), and government assistance status (32%). PRT and XRT focal groups differed on follow-up interval, shunt history, and total RT dose (all $p < .05$), whereas PRT and XRT CSI groups differed on follow-up interval, baseline neurocognitive performance score, boost volume, and CSI dose (all $p < .05$). The PRT focal group outperformed the XRT focal group on inhibition/switching ($p = .04$). The PRT CSI group outperformed the XRT CSI group on inattention/impulsivity (both $p < .05$). Several clinical variables (i.e., RT dose, boost field, baseline performance) predicted neurocognitive outcomes (all $p < .05$). The PRT focal group performed comparably to population means on most neurocognitive measures, while both CSI groups performed below expectation on multiple measures. The XRT CSI group was most impaired. All groups fell below expectation on processing speed, fine motor, and academic fluency (most $p < .01$).

Conclusions: Findings suggest generally favorable neurocognitive and academic long-term outcomes following focal PRT. Impairment was greatest following CSI regardless of modality. Dosimetry and baseline characteristics are important determinants of outcome alone or in combination with modality.

KEYWORDS
academic, brain tumor, neurocognitive, pediatric, radiation

Abbreviations: ANCOVA, analysis of covariance; CSI, craniospinal irradiation; IRB, Institutional Review Board; PRT, proton radiotherapy; RT, radiotherapy; SES, socioeconomic status; XRT, photon radiotherapy

1 | INTRODUCTION

Pediatric brain tumor survivors treated with cranial radiotherapy (RT) experience increased risk of neurocognitive impairment. Declines in global IQ[1–3] as well as in specific cognitive domains (e.g., executive function, attention, language, and fine motor control)[4–9] are commonly reported posttreatment. In addition, survivors experience worse academic outcomes, particularly on measures of academic fluency (i.e., ability to quickly complete basic reading, writing, and mathematics tasks) relative to same-age peers.[6,8,10,11]

Cognitive and academic late effects have been studied for decades in patients treated with conventional photon (or X-ray) RT (XRT). Yet, it remains unclear if newer approaches, such as proton RT (PRT), yield different neurocognitive risks. While delivering maximum radiation dose to the target volume, PRT deposits less entrance dose and no exit dose to surrounding nontarget tissue in contrast to XRT. Thus far, reports indicate that PRT provides similar disease control as compared to XRT, while potentially reducing late effects due to improved tissue sparing.[12,13]

Given the limited availability and relative novelty of PRT, studies reporting neurocognitive outcomes in pediatric brain tumor survivors treated with PRT are few. To date, only three studies have directly compared neurocognitive outcomes between pediatric brain tumor patients treated with PRT versus XRT.[14–16] A cross-sectional study found that PRT patients had higher IQs as well as processing speed scores as compared to XRT patients.[14] In two longitudinal studies,[15,16] patients treated with PRT had stable IQ trajectories, while XRT patients had significant IQ decline. IQ trajectories did not significantly differ between PRT and XRT groups in Kahalley et al. (2016), so relative neurocognitive sparing was not definitive post-PRT.[15] However, in a later study of pediatric medulloblastoma survivors, PRT patients had significantly better long-term IQ, perceptual reasoning, and working memory outcomes versus XRT. Further, XRT patients showed long-term declines in working memory and processing speed domains. However, PRT patients were not invulnerable to post-RT effects, as they also showed declines in processing speed.[16] Of note, all three studies included retrospective clinical data, where it is possible many patients underwent neurocognitive evaluation for known or expected cognitive concerns. Further, measures used to assess specific constructs (e.g., IQ) varied across participants and across evaluations, which may have limited the ability to detect group differences. Intervals from radiation to evaluation were also relatively short for the PRT group in all three studies (2.6–3.7 years). Other neurocognitive studies in this population have examined outcomes in PRT samples only or in comparison to patients who did not receive RT, without comparison to XRT-treated patients. In summary, across studies, early survivorship post-PRT has not been associated with profound neurocognitive impairment,[14–19] although younger age at PRT[15,18,19] and craniospinal irradiation (CSI)[16,17,19] are risk factors for worse cognitive outcomes, and processing speed has consistently emerged as a vulnerable neurocognitive domain post-PRT.[16–19]

To our knowledge, this is the first comparison of neurocognitive outcomes between pediatric brain tumor survivors treated with PRT versus XRT in late survivorship (7.2 years post-RT on average). We also compared academic functioning, which is an outcome with significant implications for real-world functioning[20,21] but has been understudied in this population. We hypothesized that survivors treated with PRT would outperform those treated with XRT on cognitive and academic measures, while survivors treated with CSI XRT would exhibit the greatest neurocognitive risk.

2 | METHODS AND MATERIALS

2.1 | Patients

The present study compares long-term neurocognitive and academic outcomes in pediatric brain tumor survivors treated with PRT or XRT. Patients were eligible for enrollment according to the following criteria: (1) treated with a single course of RT for a primary brain tumor with either PRT between 2007 and 2013 or XRT between 2001 and 2006, (2) no evidence of active disease at enrollment, (3) age ≥6 years at evaluation, and (4) fluent in English. The timing of treatment defined for the two groups corresponds to the shift in standard of care at our institution from XRT to PRT in 2007. Following approval from the Institutional Review Board (IRB), eligible patients were identified by medical record review and were approached consecutively for enrollment between 2011 and 2018. Informed written consent and assent were obtained prior to participation. For those patients for whom cognitive impairment prevented informed assent, consent provided by a parent or legally authorized representative was deemed sufficient by the IRB. The study achieved an 87.3% participation rate. Patients who declined participation did not differ from enrolled participants by RT type, sex, race, or histology (data not shown, all $p > .05$). Patients diagnosed with brain stem glioma, high-grade glioma, or atypical teratoid/rhabdoid tumors were excluded from participation due to our interest in long-term neurocognitive outcomes. Data were excluded for patients who could not complete testing due to profound cognitive or visual impairment ($n = 5$). The present study reports on the outcomes of 88 patients. Medical and demographic characteristics for participants are reported in Table 1.

2.2 | Measures

All participants completed a comprehensive neurocognitive battery with age-appropriate measures at the time of evaluation. Neurocognitive variables are described in Table 2. Domains assessed included full-scale IQ, verbal comprehension, perceptual reasoning, working memory, processing speed, fine motor, switching (verbal and graphomotor), inhibition/switching, verbal learning, verbal memory, visual learning, visual memory, attention, and reading, writing, and math fluency. For all measures, standardized scores (standard score,

TABLE 1 Patient characteristics by radiation treatment group

	Focal			CSI		
	PRT	XRT		PRT	XRT	
Variable	*n* (%)	*n* (%)	*p*	*n* (%)	*n* (%)	*p*
Total (*n*)	30	13		28	17	
Gender			.24			.41
Male	15 (50.0)	9 (69.2)		20 (71.4)	14 (82.4)	
Female	15 (50.0)	4 (30.8)		8 (28.6)	3 (17.7)	
Race/ethnicity			.51			.84
White	20 (66.7)	7 (53.9)		13 (46.4)	9 (52.9)	
Black	2 (6.7)	1 (7.7)		4 (14.3)	3 (17.7)	
Hispanic/Latino	6 (20.0)	5 (38.5)		7 (25.0)	4 (23.5)	
Other race*	2 (6.7)	0 (0.0)		4 (14.3)	1 (5.9)	
Government assistance	6 (20.0)	3 (23.1)	.76	13 (46.4)	6 (35.3)	.46
Histology			.68			.67
Glioma	14 (46.7)	5 (38.5)		1 (3.6)	0 (0.0)	
Medulloblastoma/PNET	2 (6.7)	1 (7.7)		17 (60.7)	12 (70.6)	
Ependymoma	8 (26.7)	6 (46.2)		0 (0.0)	0 (0.0)	
Germ cell tumor	2 (6.7)	0 (0.0)		8 (28.6)	3 (17.7)	
Other	4 (13.3)	1 (7.7)		2 (7.1)	2 (11.8)	
Tumor location			.60			.37
Supratentorial	17 (56.7)	6 (46.2)		11 (39.3)	5 (29.4)	
Infratentorial	12 (40.0)	7 (53.9)		17 (60.7)	11 (64.7)	
Both	1 (3.3)	0 (0.0)		0 (0.0)	1 (5.9)	
Craniotomy			.24			.38
No	3 (10.0)	0 (0.0)		4 (14.3)	1 (5.9)	
Yes	27 (90.0)	13 (100.0)		24 (85.7)	16 (94.1)	

(Continues)

TABLE 1 (Continued)

	Focal			CSI		
	PRT	XRT		PRT	XRT	
Variable	*n* (%)	*n* (%)	*p*	*n* (%)	*n* (%)	*p*
Shunt placement			**.04**			.45
No	25 (83.3)	7 (53.9)		18 (64.3)	9 (52.9)	
Yes	5 (16.7)	6 (46.2)		10 (35.7)	8 (47.1)	
Full posterior fossa boost						**<.01**
No	–	–	–	27 (96.4)	10 (58.8)	
Yes	–	–	–	1 (3.6)	7 (41.2)	
	Mean ± SD (range)	**Mean ± SD (range)**		**Mean ± SD (range)**	**Mean ± SD (range)**	
Karnofsky/Lansky score	88.5 ± 13.2 (50.0–100.0)	85.6 ± 10.1 (70.0–100.0)	.54	80.8 ± 15.0 (50.0–100.0)	69.2 ± 14.4 (50.0–90.0)	**.03**
Age at diagnosis (years)	6.0 ± 4.0 (1.1–16.1)	7.0 ± 3.8 (2.2–12.7)	.44	8.2 ± 4.1 (2.4–15.5)	6.0 ± 4.0 (0.9–18.0)	.08
Age RT initiated (years)	7.0 ± 4.3 (1.5–16.3)	8.1 ± 4.0 (2.8–16.0)	.47	8.5 ± 4.1 (2.9–15.5)	6.1 ± 4.0 (1.2–18.0)	.06
Age RT completed (years)	7.1 ± 4.3 (1.6–16.4)	8.2 ± 4.0 (2.9–16.1)	.46	8.6 ± 4.1 (3.0–15.6)	6.3 ± 4.0 (1.3–18.1)	.06
Age at evaluation (years)	13.4 ± 4.8 (6.1–23.5)	16.8 ± 6.4 (8.5–31.4)	.06	14.5 ± 3.8 (8.8–22.6)	16.0 ± 4.5 (10.2–30.1)	.24
Time from RT to evaluation (years)	6.3 ± 2.7 (1.2–10.6)	8.7 ± 3.4 (4.0–15.3)	**.02**	5.9 ± 3.3 (1.2–11.1)	9.8 ± 2.5 (5.8–13.9)	**<.01**
	Median (range)	**Median (range)**		**Median (range)**	**Median (range)**	
CSI dose (cGy)	–	–	–	23.4 (18.0–36.0)	30.0 (21.0–39.6)	**.04**
Total radiation dose (Gy)	50.4 (45.0–59.4)	54.0 (48.6–59.4)	**.02**	54.0 (45.0–55.8)	54.0 (30.6–55.8)	.29
Average household income median income bracket ($)	80,000–99,999 (<10,000 to >200,000)	80,000–99,999 (<10,000 to >200,000)	.46	40,000–59,999 (<10,000 to >200,000)	60,000–79,999 (<10,000 to 179,999)	.76

Note: Bold font indicates group differences with $p < .05$.

TABLE 2 Description of measures

Domain	Measure	Variable	Measure description	Original scale
Full-scale IQ	WISC-IV; WISC-V; WAIS-IV	Full-scale IQ	Composite measure of global intellectual ability	Standard score
Verbal comprehension	WISC-IV; WISC-V; WAIS-IV	Verbal Comprehension Index (VCI)	Composite measure of vocabulary, verbal reasoning skill, verbal comprehension ability, and word knowledge	Standard score
Perceptual reasoning	WISC-IV; WISC-V; WAIS-IV	Perceptual Reasoning Index (PRI)	Composite measure of visuoconstructional ability and nonverbal, fluid reasoning skill	Standard score
Working memory	WISC-IV; WISC-V; WAIS-IV	Working Memory Index (WMI)	Composite measure of ability to temporarily store and manipulate information	Standard score
Processing speed	WISC-IV; WISC-V; WAIS-IV	Processing Speed Index (PSI)	Composite measure of ability to complete simple graphomotor tasks quickly	Standard score
Fine motor	Grooved pegboard	Dominant hand	Task assessing speeded fine motor dexterity	Standard score
Switching (verbal)	DKEFS Verbal Fluency	Category switching	Measure of cognitive flexibility and rapid retrieval of words	Scaled score
Switching (graphomotor)	DKEFS Trail-Making Test	Number–letter switching	Measure of cognitive flexibility and ability to maintain cognitive sets within working memory	Scaled score
Inhibition/switching	DKEFS Color–Word Interference	Inhibition/switching	Task assessing cognitive flexibility and inhibitory control	Scaled score
Verbal learning	CVLT-C; CVLT-II	Total recall trials 1–5	Ability to learn verbal information over multiple learning trials	*T*-score
Verbal memory	CVLT-C; CVLT-II	Long delay free recall	Delayed recall of verbal information	*z*-Score
Visual learning	NEPSY-II Memory for Designs; WMS-IV Memory for Designs	Immediate recall	Immediate recall of visuospatial information	Scaled score
Visual memory	NEPSY-II Memory for Designs; WMS-IV Memory for Designs	Delayed recall	Delayed recall of visuospatial information	Scaled score
Attention				
d'	CPT-II	*d'*	Ability to discriminate between target and nontarget information	*T*-score
Omissions	CPT-II	Omissions	Measure of inattention	*T*-score
Comissions	CPT-II	Comissions	Measure of impulsivity	*T*-score
Academics				
Reading fluency	WJ-III Reading Fluency	Reading fluency	Ability to read simple sentences quickly	Standard score
Math fluency	WJ-III Math Fluency	Math fluency	Ability to quickly solve basic math facts	Standard score
Writing fluency	WJ-III Writing Fluency	Writing fluency	Ability to write simple sentences quickly	Standard score

Note: Standard scores: mean = 100, SD = 15; *T*-score: mean = 50, SD = 10; scaled score: mean = 10, SD = 3; *z*-score: mean = 0, SD = 1. Participants under the age of 17 received the WISC-IV or WISC-V, CVLT-C, and NEPSY-II, and participants 17 and older received the WAIS-IV, CVLT-II, and WMS-IV.
Abbreviations: CPT-II, Conners' Continuous Performance Test, 2nd Edition; CVLT-C, California Verbal Learning Test, Children's Edition; CVLT-II, California Verbal Learning Test, 2nd Edition; DKEFS, Delis–Kaplan Executive Function System; KCPT-II, Conners' Kiddie Continuous Performance Test, 2nd Edition; WAIS-IV, Wechsler Adult Intelligence Scale, 4th Edition; WISC-IV, Wechsler Intelligence Scale for Children, 4th Edition; WJ-III, Woodcock–Johnson III Tests of Achievement; WMS-IV, Wechsler Memory System, 4th Edition.

T-scores, scaled scores, *z*-scores) were computed using age norms. All measures were then transformed into standard scores ($M = 100$, SD = 15) to facilitate comparison across measures. Because the WISC-V does not generate a PRI score, the publisher (NCS Pearson) provided norms to calculate PRI scores in order to facilitate comparison of scores across the WISC-IV, WISC-V, and WAIS-IV. Reliabilities for the WISC-V PRI ranged from 0.93 to 0.95 for ages 6–16.[22]

2.3 | Statistical analyses

The present study utilized a cross-sectional approach to examine neurocognitive and academic scores from 88 patients at a single time point in survivorship. Mean comparisons were conducted using least square means to adjust for the contribution of a range of demographic and treatment-related covariates. Primary analyses only included

covariates on which the groups significantly differed in univariate analysis at $p < .05$. Given the known difference in neurocognitive risk between CSI and focal RT as well as our interest in accounting for significant covariates separately for these treatment groups, analyses of outcomes were conducted separately within focal and CSI groups (PRT vs. XRT in each case) using one-way analysis of covariance (ANCOVA). Tukey HSD was utilized to adjust for type one error. Group means were also compared to the standardized population mean ($M = 100$, SD = 15) using one-sample *t*-tests. The proportion of participant scores falling in the impaired range was calculated based on a cut-off standard score of 78 ($z < -1.5$). Cohen's *d*-effect sizes were calculated for each treatment group in comparison to the population mean. A small Cohen's *d*-effect size is considered $d = 0.20$, a moderate effect size is considered $d = 0.50$, and a large effect size is considered $d = 0.80$.[23]

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics by RT group are compared in Table 1. PRT and XRT groups did not significantly differ on all demographic variables, including gender, race/ethnicity, age, and socioeconomic status (SES) (i.e., government assistance status, average household income). On clinical comparisons, XRT focal patients had a longer follow-up interval (8.7 vs. 6.3 years), were more frequently shunted, and received higher total RT dose compared to PRT focal patients (all $p < .05$). More XRT CSI patients received a full posterior fossa boost compared to PRT CSI patients ($p < .01$). XRT CSI patients also had a longer follow-up interval (9.8 vs. 5.9 years), received higher CSI dose, and received lower Karnofsky/Lansky performance scores at their first follow-up clinic visit compared to PRT CSI patients (all $p < .05$). No other clinical differences were identified between RT groups.

3.2 | Population mean comparisons

Unadjusted means and standard deviations are provided in Table 3, with bold numbers indicating scores that significantly deviated from the standardized population mean ($M = 100$, SD = 15). All groups fell significantly below the population mean on measures of processing speed and fine motor coordination (most $p < .01$). On all other cognitive measures, the PRT focal group did not differ significantly from the population mean. In contrast, the XRT CSI group performed significantly below the population mean on all cognitive measures apart from attention tasks (most $p < .01$, $d > 0.8$). The XRT focal and PRT CSI groups performed significantly below the population mean with respect to FSIQ, verbal switching, and graphomotor switching ($p < .05$). The PRT CSI group also performed significantly lower than the population mean on measures of verbal learning ($p < .01$) as well as verbal memory and visual learning ($p < .05$). Regarding academic fluency, all four groups performed significantly below normative standards on measures of math and writing fluency (most $p < .01$). The PRT CSI group and both XRT groups also performed significantly below expected levels on a measure of reading fluency (all $p < .01$). Figure 1 graphically depicts the unadjusted means, demonstrating that the PRT focal group tended to receive the highest scores across most cognitive and academic measures. In contrast, the XRT CSI group tended to perform worse than the other three groups on cognitive and academic measures.

The proportion of patients with impaired performance is also presented in Table 3. More than 50% of the XRT CSI group was impaired on all three academic fluency measures and most cognitive measures. The percentage of impairment in the PRT focal group ranged from 3.3% to 33.3% across measures, with the greatest impairment observed on timed tasks and those with motor demands. Percent impairment ranged from 7.7% to 53.9% in the XRT focal group and from 10.7% to 60.7% in the PRT CSI group.

3.3 | Radiation group comparisons

ANCOVA results are provided in Table 4. When controlling for clinical variables that significantly differed between focal groups (shunt placement, total radiation dose, follow-up interval), the PRT focal group significantly outperformed the XRT focal group on a measure of inhibition and switching ($p < .05$). No significant group differences were observed on other cognitive or academic outcomes for the PRT and XRT focal groups. However, ANCOVA results identified significant effects of total radiation dose for verbal switching ($F[1,34] = 7.14$, $p = .01$) and writing fluency ($F[1,38] = 4.69$, $p = .04$) when accounting for RT group and other covariates. For the CSI groups, when controlling for clinical variables that significantly differed (Karnofsky/Lansky score, CSI dose, full posterior fossa boost, follow-up interval), the PRT CSI group significantly outperformed the XRT CSI group on measures of inattention and impulsivity (both $p < .05$). No significant group differences were observed on other cognitive or academic outcomes for the PRT and XRT CSI groups. However, several treatment-related covariates emerged as significant predictors. Full posterior fossa boost significantly predicted processing speed ($F[1,30] = 5.15$, $p = .03$), inattention (i.e., CPT *d'*) ($F[1,26] = 5.11$, $p = .03$), reading fluency ($F[1,31] = 4.90$, $p = .03$), math fluency ($F[1,31] = 4.22$, $p < .05$), and writing fluency ($F[1,31] = 8.64$, $p = .01$) within the context of the full model. Karnofsky/Lansky performance was also a significant predictor of processing speed ($F[1,30] = 4.61$, $p = .04$), inhibition/shifting ($F[1,27] = 9.59$, $p < .01$), and writing fluency ($F[1,31] = 5.57$, $p = .02$) for the CSI groups when accounting for RT group and other covariates in the full model.

4 | DISCUSSION

This study provides further evidence of good outcomes following focal PRT, consistent with extant research.[14,15,24] Patients treated with focal PRT performed within normal limits on most cognitive and academic

TABLE 3 Unadjusted means, norm comparisons, and percent impairment by treatment group

	Focal										CSI									
	PRT					XRT					PRT					XRT				
Variable	*M* (SD)	*t*	*p*	*d*	Impaired %	*M* (SD)	*t*	*p*	*d*	Impaired %	*M* (SD)	*t*	*p*	*d*	Impaired %	*M* (SD)	*t*	*p*	*d*	Impaired %
FSIQ	99.5 (15.9)	0.16	.88	0.03	13.3	**89.7 (12.7)**	2.07	**.04**	0.69	15.4	**87.7 (19.5)**	3.16	**.00**	0.81	28.6	***68.3 (18.0)***	7.31	**<.01**	2.11	76.5
VCI	103.2 (12.0)	-1.10	.27	0.21	3.3	96.6 (14.7)	0.69	.49	0.23	15.4	91.8 (20.1)	2.05	.05	0.54	28.6	***76.8 (15.5)***	5.37	**<.01**	1.55	64.7
PRI	104.3 (17.7)	-1.46	.14	0.29	10.0	92.4 (17.7)	1.51	.13	0.50	23.1	92.0 (22.8)	1.77	.09	0.53	17.9	***78.5 (19.7)***	4.96	**<.01**	1.43	58.8
WMI	97.0 (16.2)	1.02	.31	0.20	10.0	97.7 (9.7)	0.47	.64	0.16	15.4	**91.7 (18.9)**	2.75	**.01**	0.55	17.9	***72.1 (19.2)***	6.44	**<.01**	1.85	76.5
PSI	***89.0 (18.6)***	3.75	**<.01**	0.73	30.0	***76.9 (11.7)***	4.62	**<.01**	1.54	46.2	***78.8 (12.9)***	6.93	**<.01**	1.42	46.4	***66.8 (13.0)***	7.68	**<.01**	2.22	82.4
Fine motor	**89.9 (23.8)**	2.21	**.04**	0.66	26.7	***75.1 (15.8)***	4.98	**<.01**	1.66	53.9	***66.3 (34.3)***	4.81	**<.01**	2.15	60.7	***44.2 (39.2)***	4.93	**<.01**	3.61	82.4
Switching (verbal)	100.2 (22.8)	-0.05	.96	0.01	26.7	**82.8 (16.8)**	3.44	**<.01**	1.15	38.5	**92.4 (14.4)**	2.43	**.02**	0.51	17.9	***79.6 (20.3)***	4.52	**<.01**	1.36	64.7
Switching (graphomotor)	95.5 (19.8)	1.08	.29	0.30	30.0	***80.6 (14.2)***	3.89	**<.01**	1.30	38.5	***80.7 (17.3)***	6.18	**<.01**	1.29	46.4	***70.5 (19.8)***	6.53	**<.01**	1.96	76.5
Inhibition/switching	99.8 (14.7)	0.07	.94	0.01	23.3	**80.0 (21.2)**	4.00	**<.01**	1.33	38.5	94.6 (17.3)	1.70	.09	0.36	32.1	***75.0 (17.5)***	5.52	**<.01**	1.66	58.8
Verbal learning	102.5 (19.3)	-0.67	.51	0.17	20.0	92.0 (19.9)	1.60	.11	0.53	30.8	**88.8 (19.4)**	2.88	**.01**	0.74	32.1	**82.0 (21.3)**	2.93	**.01**	1.19	52.9
Verbal memory	101.4 (20.5)	-0.36	.72	0.09	16.7	90.8 (18.7)	1.83	.07	0.61	23.1	**90.4 (22.1)**	2.17	**.04**	0.63	21.4	***78.8 (21.7)***	3.40	**.01**	1.41	64.7
Visual learning	101.5 (18.5)	-0.52	.60	0.10	10.0	96.1 (20.9)	0.78	.44	0.26	15.4	**90.0 (21.3)**	2.34	**.03**	0.66	25.0	***72.3 (14.2)***	6.13	**<.01**	1.85	76.5
Visual memory	104.2 (19.8)	-1.09	.29	0.28	13.3	101.7 (19.0)	-0.33	.74	0.11	7.7	95.8 (17.1)	1.40	.16	0.28	14.3	***76.8 (12.5)***	5.12	**<.01**	1.55	64.7
Attention																				
d'	104.0 (15.7)	-1.34	.18	0.26	13.3	97.5 (8.1)	0.44	.66	0.17	23.1	101.0 (14.80)	-0.30	.76	0.06	17.9	97.2 (18.6)	0.59	.55	0.19	11.8
Omissions	95.2 (16.6)	1.64	.10	0.32	3.3	93.1 (20.3)	1.23	.22	0.47	15.4	95.5 (18.0)	1.40	.16	0.30	10.7	**88.3 (20.6)**	2.47	**.01**	0.78	11.8
Comissions	104.2 (15.0)	-1.41	.16	0.28	16.7	100.1 (9.0)	-0.01	.99	0.00	15.4	102.8 (15.3)	-0.88	.38	0.19	21.4	97.0 (13.7)	0.63	.53	0.20	11.8
Academics																				
Reading fluency	**93.3 (18.0)**	2.17	**.03**	0.44	23.3	***77.6 (8.3)***	4.49	**<.01**	1.50	46.2	***80.6 (19.6)***	6.44	**<.01**	1.28	42.9	***67.2 (18.6)***	7.58	**<.01**	2.18	82.4
Math fluency	***89.5 (17.4)***	3.50	**<.01**	0.70	33.3	***80.1 (13.8)***	3.98	**<.01**	1.33	30.8	***80.6 (15.6)***	6.44	**<.01**	1.29	42.9	***63.6 (14.6)***	8.41	**<.01**	2.43	88.2
Writing fluency	**91.7 (20.9)**	2.89	**.00**	0.55	26.7	***83.6 (12.8)***	3.29	**<.01**	1.10	38.5	***81.2 (18.0)***	6.24	**<.01**	1.24	53.6	***67.2 (16.8)***	7.58	**<.01**	2.19	82.4

Note: All unadjusted means are provided in standard scores ($M = 100$, $SD = 15$). Means that differ significantly from the population mean at $p < .05$ are given in bold. Means that are in bold and italicized differ from the population mean at $p < .01$. Cohen's *d*-effect sizes are calculated using the group mean and population means as well as their respective standard deviations. All effect sizes are absolute values. The percentage of participants impaired was based on a cut-off standard score of 78 ($z < -1.5$).

Abbreviations: FSIQ, full-scale intelligence quotient; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WMI, Working Memory Index.

TABLE 4 Long-term neurocognitive and academic outcomes by treatment group

	Focal					CSI				
	PRT	XRT				PRT	XRT			
Variable	*M* (SE)	*M* (SE)	*df*	*F*	*p*	*M* (SE)	*M* (SE)	*df*	*F*	*p*
FSIQ	98.0 (2.7)	92.5 (4.3)	1,37	1.01	.32	86.3 (4.5)	71.3 (7.3)	1,31	2.42	.13
VCI	101.8 (2.2)	101.4 (3.6)	1,36	0.00	.95	90.2 (4.4)	80.0 (7.1)	1,31	1.20	.28
PRI	103.6 (3.2)	96.3 (5.1)	1,37	1.32	.26	92.7 (5.2)	76.9 (8.4)	1,31	2.06	.16
WMI	96.4 (2.9)	95.8 (4.5)	1,37	0.01	.92	89.0 (4.4)	77.8 (7.1)	1,31	1.45	.24
PSI	87.9 (3.2)	78.5 (5.1)	1,37	2.17	.15	76.0 (2.8)	72.3 (4.4)	1,30	0.40	.53
Fine motor	89.3 (4.2)	81.4 (6.8)	1,38	0.88	.36	63.3 (8.2)	50.1 (12.9)	1,30	0.59	.45
Switching (verbal)	96.6 (3.9)	87.5 (5.9)	1,34	1.44	.24	90.6 (4.0)	83.0 (6.5)	1,27	0.74	.40
Switching (graphomotor)	93.7 (4.0)	87.5 (5.8)	1,33	0.69	.41	82.6 (4.5)	66.5 (7.5)	1,28	2.59	.12
Inhibition/switching	96.9 (3.8)	81.5 (5.7)	1,34	4.43	**.04**	90.6 (4.0)	83.0 (6.5)	1,27	0.74	.40
Verbal learning	99.3 (3.9)	93.3 (6.1)	1,37	0.61	.44	87.0 (4.5)	85.7 (7.3)	1,31	0.02	.90
Verbal memory	99.3 (3.9)	92.8 (6.1)	1,37	0.70	.41	89.7 (4.9)	80.1 (8.0)	1,31	0.83	.37
Visual learning	101.0 (3.6)	87.3 (6.0)	1,36	3.43	.07	87.4 (4.7)	81.7 (7.6)	1,31	0.31	.58
Visual memory	102.8 (3.7)	96.1 (6.1)	1,36	0.76	.39	93.1 (3.7)	85.6 (6.0)	1,31	0.90	.35
Attention										
d'	104.8 (3.0)	92.7 (5.3)	1,35	3.48	.07	93.47 (3.6)	115.06 (6.3)	1,26	6.74	**.02**
Omissions	95.3 (3.5)	90.5 (6.3)	1,35	0.39	.54	104.07 (4.9)	112.61 (8.4)	1,26	0.59	.45
Comissions	103.5 (2.8)	97.1 (4.9)	1,35	1.13	.30	93.55 (3.7)	110.95 (6.3)	1,26	4.33	**.05**
Academics										
Reading fluency	92.2 (3.0)	81.1 (4.6)	1,35	3.51	.07	77.6 (4.3)	73.6 (6.9)	1,31	0.19	.67
Math fluency	87.0 (3.3)	84.1 (5.1)	1,36	0.20	.66	77.0 (3.4)	71.2 (5.5)	1,31	0.65	.43
Writing fluency	89.7 (3.4)	87.9 (5.4)	1,38	0.07	.80	76.3 (3.6)	77.4 (5.7)	1,31	0.02	.89

Note: All results are provided in standard scores ($M = 100$, $SD = 15$). Results depict least square means adjusting for covariates (focal group covariates: shunt, interval between RT and evaluation, and total radiation dose; CSI group covariates: posterior fossa boost, Lansky/Karnofsky score, interval between RT and evaluation, and CSI dose). Bold font indicates group differences with $p < .05$.

Abbreviations: FSIQ, Full-Scale Intelligence Quotient; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WMI, Working Memory Index.

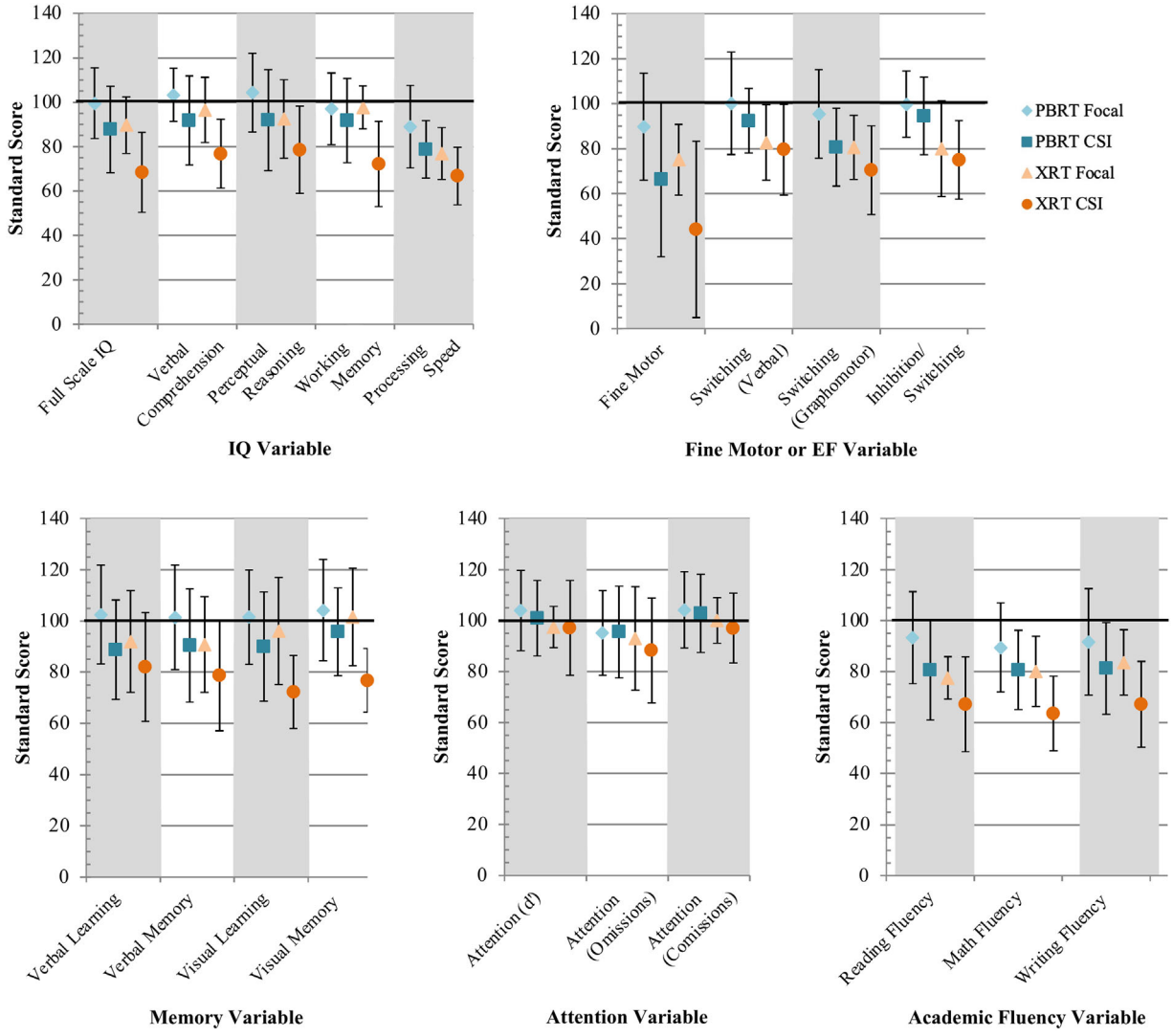

FIGURE 1 Performance on cognitive and academic measures across groups. Population mean for all measures is a standard score of 100 with a standard deviation of 15

measures and generally performed comparably to normative samples of typically developing children. Even weaknesses in processing speed, fine motor, and academic fluency skills fell just below the average range, indicating clinically mild challenges in these areas for this group.

In contrast, the focal XRT group performed worse than expected for age on global intellectual functioning, cognitive domains traditionally associated with RT late effects (processing speed, fine motor, executive functioning), and academic fluency skills. While comparisons of PRT and XRT focal groups (controlling for covariates) only found significant group differences on a measure of executive functioning, this implicates increased risk for daily living challenges in XRT focal patients, as executive dysfunction predicts poorer long-term adaptive functioning skills (e.g., social skills, community independence) in survivors.[25] Of note, total radiation dose differed between focal groups and predicted switching and writing fluency skills, indicating that dosimetry impacted some domains of functioning regardless of radiation modality. In general, however, we may have been underpowered to detect differences between focal groups. Alternatively, advanced XRT techniques may provide enough conformality that there is no measurable cognitive advantage of PRT for focal radiation.

It is well documented that CSI radiation confers the greatest neurocognitive risk.[5,15] The XRT CSI group in this study was particularly impaired, with 76% exhibiting clinically impaired global intellectual functioning and 53–88% demonstrating impaired performance across all cognitive and academic fluency tasks (except a computerized attention task). This group's performance is lower than published literature (e.g., reported group FSIQ means range from 82 to 87[1,14]). This may be due, in part, to the longer follow-up interval in the present study (9.8 years vs. 5.2[1] to 6.7[14] years), as cognitive functioning appears to decline over time in XRT CSI patients,[2,26] or because long-term clinical follow-up in our cancer center or participation in this type of study may attract survivors with significant cognitive concerns or ongoing challenges.

The proton CSI group also showed below-average performance in general intellectual functioning and cognitive domains traditionally sensitive to RT (e.g., working memory, processing speed, fine motor, executive functioning, memory), consistent with some existing proton outcomes research,[17,24] as well as academic fluency tasks. A smaller proportion of the PRT CSI group performed in the impaired range on these measures versus XRT CSI, with 29% demonstrating impaired FSIQ and 14–60% in the impaired range across cognitive and academic fluency measures (except for attention), suggesting broadly better outcomes within the PRT CSI group. However, after accounting for covariates, the only statistically significant difference between XRT and PRT CSI groups was on a measure of attention. Notably, the groups differed on clinical variables (i.e., boost volume, CSI dose, follow-up interval, Karnofsky/Lansky scores), which, themselves, are associated with greater cognitive risk.[2,15,27,28] Indeed, baseline Karnofsky/Lansky performance scores (an indicator of general performance status at the first postoperative outpatient clinic visit) and receiving a boost to the full posterior fossa (rather than to the tumor bed and margin only) significantly predicted a range of outcomes within the CSI group, emphasizing the role of radiation field and early functional outcomes (and potentially surgical complications) in predicting long-term cognitive outcomes independent of treatment modality. While superior cognitive outcomes have been detected with PRT compared to XRT in a homogenous sample (medulloblastoma only) treated with CSI according to the same protocols,[16] the diagnostic heterogeneity of the present sample and differences in radiation field between groups may have prevented our ability to detect differences in cognitive outcomes attributable to RT modality.

Of note, academic fluency, processing speed, and fine motor coordination emerged as areas of relative weakness across all RT groups, including PRT focal. Processing speed was the lowest index on standardized intelligence measures for all groups and likely contributed to the full-scale intelligence quotient deviating from the population mean in the XRT focal and PRT CSI groups, particularly given relatively preserved performance on measures of verbal comprehension and perceptual reasoning. The processing speed findings are consistent with recent research,[17–19] but conflict with findings by Gross et al. (2019) that documented processing speed within normal limits (i.e., standard score ≥90) for the PRT focal group. This is perhaps a minor difference given the relatively large standard deviation in the present study and the comparably large confidence interval in the Gross et al. (2019) study. Thus, these differences may be the product of small sample sizes and limited power. Of note, academic fluency and processing speed tasks all involved fine motor demands, so lower performance on these tasks may be attributable in part to fine motor limitations (although fine motor demands for reading fluency were minimal). Nevertheless, academic fluency supports more advanced academic skills (e.g., reading comprehension, math problem solving, written expression) by freeing cognitive resources to complete complex tasks.[29–31] Thus, broader academic skill development may be at risk in survivors, particularly in treatment groups (both CSI groups, XRT focal) with difficulties in executive functioning domains that support academic growth.[32–34] Our results suggest that academic fluency, processing speed, and fine motor dexterity warrant continued close monitoring in survivors, regardless of RT modality and technique.

Compared to previous work,[14–16] the present study has several methodological advantages that improve generalizability of findings. First, this study has a longer follow-up interval as compared to extant research.[14–16] Next, while previous studies utilized clinical data from patients referred for evaluation,[14–16] patients on this study received standard research assessment independent of clinical concerns or referrals. Third, SES did not differ between groups, in contrast to Gross et al. (2019). As lower SES is itself associated with cognitive and academic risks,[35–37] group differences in SES complicate interpretation of cognitive and academic differences.

Several study limitations should be considered. Families with greater concerns about a patient's cognitive functioning may have been more likely to participate. Similarly, patients with worse outcomes may be more likely to stay engaged in follow-up in pediatric oncology centers, which may have resulted in a more impaired sample, particularly in the XRT CSI group. Patients were not randomized to RT groups given the practical and ethical barriers preventing such randomized controlled trials. The sample size is relatively small, and the sample is heterogeneous in terms of medical variables (e.g., tumor type, location, chemotherapies). While we attempted to minimize differences in follow-up interval by examining the last available cohort of XRT patients and comparing these patients to the first available cohort of PRT patients, PRT patients were treated more recently than XRT patients and, consequently, there was less time for late effects to emerge. There is also the potential that treatment differences across groups (e.g., reductions in boost volume, changes in chemotherapy regimens, advancements in surgical procedures) influenced outcomes to some extent. Further, as the study is cross-sectional, we are limited in our ability to extrapolate changes in cognitive functioning over time. Finally, PRT is likely a surrogate for lower brain dose. To best understand any relative cognitive advantage realized from PRT and to inform treatment planning, future research should examine associations between specific brain region/structure dosimetry and cognitive skill development.

5 | CONCLUSIONS

Overall, survivors treated with CSI are at greatest cognitive and academic risk, although risks may be less with PRT CSI versus XRT CSI. While differences between focal groups were less definitive in this study, age-appropriate performance within the focal PRT group on nearly all measures indicates generally good outcomes following treatment. Regardless of RT dose, field, and modality, survivors of pediatric brain tumor require neurocognitive surveillance, as recommended in the Children's Oncology Group survivorship guidelines,[38] to ensure timely identification of deficits and provision of appropriate accommodations and services.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Amanda E. Child https://orcid.org/0000-0002-0616-6509

Arnold C. Paulino https://orcid.org/0000-0002-0269-3045

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